Care Med., 19 Suppl. 2: S54-57 (1993), which is a review of the role of insulin, GH, and IGF-I as anabolic agents in the critically ill. IGF-I has hypoglycemic effects similar to those of insulin, but also promotes positive nitrogen balance (Underwood *et al.*, Hormone Res., 24: 166 (1986); Guler *et al.*, N. Engl. J. Med., 317: 137 (1987)). Due to this range of activities, IGF-I is being tested in humans for such widely disparate uses as wound healing, treatment of diabetes, reversal of whole body catabolic states, treatment of heart conditions such as congestive heart failure, and treatment of neurological disorders (Guler *et al.*, Proc. Natl. Acad. Sci. USA, 85: 4889-4893 (1988); Duerr *et al.*, J. Clin. Invest., 95: 619-627 (1995); and Barinaga, Science, 264: 772-774 (1994)).

3. Replace the first full paragraph on page 5 (lines 7-20) with the following paragraph:

The administration of rhIGF-I to Type II diabetics, as reported by Schalch *et al.*, J. Clin. Endo. Metab., 77: 1563-1568 (1993), demonstrated a fall in both serum insulin as well as a paralleled decrease in C peptide levels. This indicated a reduction in pancreatic insulin secretion after five days of IGF-I treatment. This effect has been independently confirmed by Froesch *et al.*, Horm. Res., 42: 66-71 (1994). *In vivo* studies in normal rats also illustrate that IGF-I infusion inhibits pancreatic insulin release (Furnsinn *et al.*, Endocrinology, 135: 2144-2149 (1994)). In addition, in pancreas perfusion preparations, IGF-I also suppressed insulin secretion (Leahy *et al.*, Endocrinology, 126: 1593-1598 (1990)). Despite these clear *in vivo* inhibitory effects of IGF-I on insulin secretion in humans and animals, *in vitro* studies have not yielded such uniform results.

4. Replace the paragraph on page 5 beginning at line 21 and ending on page 6, line 11 with the following paragraph:

RhIGF-I has the ability to improve insulin sensitivity. For example, rhIGF-I (70 μg/kg bid) improved insulin sensitivity in non-diabetic, insulin-resistant patients with myotonic dystrophy (Vlachopapadopoulou *et al.*, J. Clin. Endo. Metab., 80: 3715-3723 (1995)). Saad *et al.*, Diabetologia, 37: Abstract 40 (1994) reported dose-dependent improvements in insulin sensitivity in adults with obesity and impaired glucose tolerance following 15 days of rhIGF-I treatment (25 μg and 100 μg/kg bid). RhIGF-I also improved insulin sensitivity and glycemic control in some

patients with severe type A insulin resistance (Schoenle *et al.*, Diabetologia, 34: 675-679 (1991); Morrow *et al.*, Diabetes, 42 (Suppl.): 269 (1993) (abstract); Kuzuya *et al.*, Diabetes, 42: 696-705 (1993)) and in other patients with non-insulin dependent diabetes mellitus (Schalch *et al.*, "Short-term metabolic effects of recombinant human insulin-like growth factor I (rhIGF-I) in type II diabetes mellitus", in: Spencer EM, ed., Modern Concepts of Insulin-like Growth Factors (New York: Elsevier: 1991) pp. 705-713; Zenobi *et al.*, J. Clin. Invest., 90: 2234-2241 (1992)).

5. Replace the paragraph on page 6 beginning at line 12 and ending on page 7, line 8 with the following paragraph:

A general scheme for the etiology of some clinical phenotypes that give rise to insulin resistance and the possible effects of administration of IGF-I on selected representative subjects is given in several references. See, *e.g.*, Elahi *et al.*, "Hemodynamic and metabolic responses to human insulin-like growth factor-1 (IGF-I) in men," in: Modern Concepts of Insulin-Like Growth Factors, (Spencer, EM, ed.), Elsevier, New York, pp. 219-224 (1991); Quin *et al.*, New Engl. J. Med., 323: 1425-1426 (1990); Schalch *et al.*, "Short-term metabolic effects of recombinant human insulin-like growth factor 1 (rhIGF-I) in type 11 diabetes mellitus," in: Modern Concepts of Insulin-Like Growth Factors, (Spencer, EM, ed.), Elsevier, New York, pp. 705-713 (1991); Schoenle *et al.*, Diabetologia, 34: 675-679 (1991); Usala *et al.*, N. Eng. J. Med., 327: 853-857 (1992); Lieberman *et al.*, J. Clin. Endo. Metab., 75: 30-36 (1992); Zenobi *et al.*, J. Clin. Invest., 90: 2234-2241 (1992); Zenobi *et al.*, J. Clin. Invest., 89: 1908-1913 (1992); Kerr *et al.*, J. Clin. Invest., 91: 141-147 (1993). When IGF-I was used to treat Type II diabetic patients in the clinic at a dose of 120-160 μg/kg twice daily, the side effects outweighed the benefit of the treatment (Jabri *et al.*, Diabetes, 43: 369-374 (1994)). See also Wilton, Acta Paediatr., 383: 137-141 (1992) regarding side effects observed upon treatment of patients with IGF-I.

6. Replace the last paragraph beginning at page 14, line 25 and ending on page 15, line 6 as follows:

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Accordingly, the present invention relates, in a first embodiment, to a peptide comprising the following sequence:

$Xaa_{(1-4)}CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}Xaa_{(10)}Xaa_{(11)}Xaa_{(12)}Xaa_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}$ $Xaa_{(18)}$ (SEQ ID NO:1), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind, $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently any amino acid, $Xaa_{(10)}$ and $Xaa_{(13)}$ are independently Leu or Nle, and $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met.

7. Replace the last paragraph on page 15 (lines 12-27) as follows:

In another preferred embodiment, this peptide comprises the following sequence:

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$CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}Xaa_{(10)}Xaa_{(11)}TrpXaa_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:3). More preferably, such peptide comprises one of the following sequences:

CysArgAlaGlyAlaLeuGlnTrpLeuCysGluLysTyrPhe (SEQ ID NO:4);

CysArgAlaGlyArgLeuGlnTrpLeuCysGluLysTyrPhe (SEQ ID NO:5);

CysArgAlaGlyAsnLeuGlnTrpLeuCysGluLysTyrPhe (SEQ ID NO:6);

CysArgAlaGlyProNleGlnTrpLeuCysGluLysTyrPhe (SEQ ID NO:7);

CysArgAlaGlyProLeuGlnTrpNleCysGluLysTyrPhe (SEQ ID NO:8);

CysArgAlaGlyProLeuGlnArgLeuCysGluLysTyrPhe (SEQ ID NO:9);

CysArgAlaGlyProLeuGlnNal(1)LeuCysGluLysTyrPhe (SEQ ID NO:10); or

CysArgAlaGlyProLeuGlnHisLeuCysGluLysTyrPhe (SEQ ID NO:11).

8. Replace the first paragraph on page 18 (lines 1-7) as follows:

In another aspect of the invention, the above peptide having SEQ ID NO:1 or SEQ ID NO:3

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has a C-terminal fusion comprising the following sequence:

GlyGlyGlySerGlyGlyAlaGlnHisAspGluAlaValAspAsnLysPheAsnLysGlu GlnGlnAsnAlaPheTyrGluIleLeuHisLeuProAsnLeuAsnGluGluGlnArgAsnAlaPheIleGlnSerLeuL ysAspAspProSerGlnSerAlaAsnLeuLeuAlaGluAlaLysLysLeuAsnAspAlaGlnAlaProAsnValAsp

MetAsn (SEQ ID NO:30).

9. Replace the last paragraph beginning at page 29, line 20 and ending on page 30, line 18 as follows:

B9 A "disorder" is any condition that would benefit from treatment with an IGF, including but not limited to, for example, lung diseases, hyperglycemic disorders as set forth below, renal disorders, such as acute and chronic renal insufficiency, end-stage chronic renal failure, glomerulonephritis, interstitial nephritis, pyelonephritis, glomerulosclerosis, *e.g.,* Kimmelstiel-Wilson in diabetic patients and kidney failure after kidney transplantation, obesity, GH-insufficiency, Turner's syndrome, Laron's syndrome, short stature, undesirable symptoms associated with aging such as obesity and increased fat mass-to-lean ratios, immunological disorders such as immunodeficiencies including decreased CD4 counts and decreased immune tolerance or chemotherapy-induced tissue damage, bone marrow transplantation, diseases or insufficiencies of cardiac structure or function such as heart dysfunctions and congestive heart failure, neuronal, neurological, or neuromuscular disorders, *e.g.,* peripheral neuropathy, multiple sclerosis, muscular dystrophy, or myotonic dystrophy, and catabolic states associated with wasting caused by any condition, including, *e.g.,* trauma or wounding or infection such as with a bacterium or human virus such as HIV, wounds, skin disorders, gut structure and function that need restoration, and so forth. The disorder being treated may be a combination of two or more of the above disorders. The preferred disorders targeted for treatment herein are diabetes and obesity, heart dysfunctions, kidney disorders, neurological disorders, whole body growth disorders, and immunological disorders.

10. Replace the second paragraph on page 42 (lines 10-18) as follows:

B10 The present invention relates to various classifications of peptides having the function of displacing IGFBP-1. In one embodiment, the peptide comprises the following sequence:

$Xaa_{(1-4)}CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}Xaa_{(10)}Xaa_{(11)}Xaa_{(12)}Xaa_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}$
$Xaa_{(18)}$ (SEQ ID NO:1), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind,

$Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently any amino acid, $Xaa_{(10)}$ and $Xaa_{(13)}$ are independently Leu or Nle, and $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met.

11. Replace the last paragraph beginning at page 42, line 19 and ending on page 43, line 2 as follows:

Preferably, in SEQ ID NO:1 above, $Xaa_{(1-4)}$, $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently Ala, Leu, Ile, Glu, Arg, Val, Gly, Gln, Ser, Met, Pro, Thr, Asn, Lys, or Trp, more preferably Ala, Glu, Arg, Val, Gly, Gln, Ser, Pro, Asn, or Lys. Independently, or in combination with this, preferably $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Phe, Trp, Tyr, Pro, Gln, or Met, more preferably Phe, Trp, or Tyr, and most preferably Phe or Trp. Independently, or in combination with this, $Xaa_{(9)}$ is Ala, Arg, Asn, or Pro. In more preferred embodiments, $Xaa_{(6)}$ is Arg, $Xaa_{(7)}$ is Ala, $Xaa_{(9)}$ is Pro, $Xaa_{(11)}$ is Gln, $Xaa_{(12)}$ is Trp, $Xaa_{(15)}$ is Glu, $Xaa_{(16)}$ is Lys, $Xaa_{(17)}$ is Tyr, and/or $Xaa_{(18)}$ is Phe.

12. Replace second paragraph on page 43 (lines 7-10) as follows:

Another preferred set of peptides comprising SEQ ID NO:1 is $CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}Xaa_{(10)}Xaa_{(11)}TrpXaa_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:3). More specifically preferred such peptides comprise one of the following sequences: SEQ ID NO:4, 5, 6, 7, 8, 9, 10, or 11.

13. Replace the last paragraph beginning at page 43, line 22 and ending on page 44, line 4 with two paragraphs as follows:

The most preferred of those peptides comprising SEQ ID NO:1 comprise one of the following sequences: SEQ ID NO:4, 5, 6, 7, 8, 9, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29. In another preferred aspect, the peptide comprising SEQ ID NO:1 has a C-terminal fusion (e.g., a sequence attached to C-terminal residue $Xaa_{(18)}$) comprising the following

sequence:

GlyGlyGlySerGlyGlyAlaGlnHisAspGluAlaValAspAsnLysPheAsnLysGlu GlnGlnAsnAlaPheTyrGluIleLeuHisLeuProAsnLeuAsnGluGluGlnArgAsnAlaPheIleGlnSerLeuLysAspAspProSerGlnSerAlaAsnLeuLeuAlaGluAlaLysLysLeuAsnAspAlaGlnAlaProAsnValAspMetAsn (SEQ ID NO:30).

14. Replace the last paragraph beginning at page 44, line 22 and ending on page 45, line 4 as follows:

In another embodiment, the invention provides a peptide comprising the following sequence: $Xaa_{(1-4)}Xaa_{(5)}Xaa_{(6-7)}$ProLeuGlu$Xaa_{(11)}$LeuAla$Xaa_{(14)}Xaa_{(15)}Xaa_{(16)}Xaa_{(17)}GluXaa_{(19)}$ (SEQ ID NO:32), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind; $Xaa_{(5)}$ is any amino acid, $Xaa_{(6-7)}$ is absent or is between 1 and 2 amino acids, $Xaa_{(14)}$ and $Xaa_{(15)}$ are independently any amino acid, $Xaa_{(11)}$ and $Xaa_{(16)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met, $Xaa_{(17)}$ is absent or is Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met, and $Xaa_{(19)}$ is absent or is Gly.

15. Replace the first full paragraph on page 85 (lines 5-18) as follows:

With regard to construction of the delivery device, any form of aerosolization known in the art, including but not limited to nebulization, atomization, or pump aerosolization of a liquid formulation, and aerosolization of a dry powder formulation, can be used in the practice of the invention. A delivery device that is uniquely designed for administration of solid formulations is envisioned. Often, the aerosolization of a liquid or a dry powder formulation will require a propellent. The propellent may be any propellant generally used in the art. Specific nonlimiting examples of such useful propellants include a chlorofluorocarbon, a hydrofluorocarbon, a hydrochlorofluorocarbon, or a hydrocarbon, including trifluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof.

16. Replace the last paragraph beginning at page 86, line 20 and ending on page 87, line 2

as follows:

The liquid aerosol formulation may include a carrier. The carrier is a macromolecule that is soluble in the circulatory system and that is physiologically acceptable where physiological acceptance means that those of skill in the art would accept injection of said carrier into a patient as part of a therapeutic regime. The carrier preferably is relatively stable in the circulatory system with an acceptable plasma half life for clearance. Such macromolecules include but are not limited to soya lecithin, oleic acid, and sorbitan trioleate, with sorbitan trioleate preferred.

17. Replace the last paragraph beginning at page 96, line 22 and ending on page 97, line 7 as follows:

W8 was also completely conserved in IGFBP-1 selected peptide-phage libraries, although the alanine substitution had a smaller effect on binding than in the case of L6 or L9. Therefore, several large side-chain substitutions were tested at this position. Interestingly, arginine, 1-naphthylalanine (Nal(1)), or histidine substitutions (bp1-22, bp1-23, and bp1-24, respectively) each had modest (<10-fold) effects on IGFBP-1 binding affinity (Table I).

From these experiments, a new consensus sequence for IGFBP-1 binding may be formulated as follows:

$CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}Xaa_{(10)}Xaa_{(11)}TrpXaa_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:3), where $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently any amino acid, $Xaa_{(10)}$ and $Xaa_{(13)}$ are independently Leu or Nle, and $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met.

18. Replace Table I on page 97 (lines 8-28) as follows:

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Table I

Relative affinities of bp1-16 variants measured by ELISA or BIAcore™(*) inhibition assays

bp1-16 Variant	Peptide Sequence	Fold potency reduction IC_{50}(mut)/IC_{50}(bp1-16)
bp1-16	CRAGPLQWLCEKYF (SEQ ID NO:37)	-1-
bp1-29	CRAAPLQWLCEKYF (SEQ ID NO:38)	50
bp1-30	CRAGALQWLCEKYF (SEQ ID NO:4)	1.5
bp1-31	CRAGRLQWLCEKYF (SEQ ID NO:5)	2.0
bp1-34	CRAGNLQWLCEKYF (SEQ ID NO:6)	3.1
bp1-32	CRAGPRQWLCEKYF (SEQ ID NO:39)	>1000
bp1-36	CRAGPXQWLCEKYF (SEQ ID NO:7), where the underlined X is Nle	6.9
bp1-26	CRAGPLQWRCEKYF (SEQ ID NO:40)	>570
bp1-37	CRAGPLQWXCEKYF (SEQ ID NO:8), where the underlined X is Nle	1.7
bp1-22	CRAGPLQRLCEKYF (SEQ ID NO:9)	3.3*
bp1-23	CRAGPLQXLCEKYF (SEQ ID NO:10), where the underlined X is Nal(1)	4.8*
bp1-24	CRAGPLQHLCEKYF (SEQ ID NO:11)	7.5

19. Replace the last paragraph on page 107 (lines 16-27) as follows:

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An improved consensus sequence for IGFBP-1 binding peptides is expected therefore to be:

$Xaa_{(1-4)}CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}Xaa_{(10)}Xaa_{(11)}Xaa_{(12)}Xaa_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}$ $Xaa_{(18)}$ (SEQ ID NO:1), wherein $Xaa_{(1-4)}$ is absent or is between 1 and 4 amino acids of any kind, $Xaa_{(6)}$, $Xaa_{(7)}$, $Xaa_{(9)}$, $Xaa_{(11)}$, $Xaa_{(15)}$, and $Xaa_{(16)}$ are independently any amino acid, $Xaa_{(10)}$ and $Xaa_{(13)}$ are independently Leu or Nle, and $Xaa_{(12)}$, $Xaa_{(17)}$, and $Xaa_{(18)}$ are independently Nal(1), His, Phe, Trp, Tyr, Pro, Gln, or Met. As noted in Example 1, truncation of the amino-terminal 4 residues ($Xaa_{(1-4)}$) has only a small effect on activity, giving a shorter consensus that still retains binding:

$CysXaa_{(6)}Xaa_{(7)}GlyXaa_{(9)}Xaa_{(10)}Xaa_{(11)}TrpXaa_{(13)}CysXaa_{(15)}Xaa_{(16)}Xaa_{(17)}Xaa_{(18)}$ (SEQ ID NO:3).

20. Replace Table VI on page 110 (lines 12-20) as follows:

Table VI

Peptide sequences for *E. coli* biosynthesis

Construct	Peptide sequence
bp1-625-Z	GQQSCAAGPLQWLCEHYFSTYGRGGGSGGAQHDEAVDNK FNKE QQNAFYEILHLPNLNEEQRNAFIQSLKDDPSQSANLLAEAK KLN DAQAPNVDMN (SEQ ID NO:51)
bp1-625	GQQSCAAGPLQWLCEHYFSTYGR (SEQ ID NO:29)

IN THE CLAIMS:

Please cancel claims 1-26, 45, and 47-51 without prejudice.